The Rejection of Claims 2-8 Under 35 U.S.C. § 112, first paragraph

Claims 2-8 remain rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not adequately described in the specification. Applicants respectfully traverse this rejection.

The purpose of the written description requirement of 35 U.S.C. § 112, first paragraph, is to convey to the skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 111, 1117 (Fed. Cir. 1991). A proper written description analysis must, therefore, begin with a correct interpretation of the claimed invention: "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Claim 2 is directed to preparations of antibodies that specifically bind to a human APC protein that is the product of a mutant allele found in a tumor and do not specifically bind to other human proteins. The human APC protein is a mutant form of the amino acid sequence shown in SEQ ID NO:2 or 7, and the mutant allele is a mutant form of the nucleotide sequence shown in SEQ ID NO:1. The mutant allele can contain, for example, a mutation selected from the group consisting of mutations at codons 243, 279, 288, 331, 413, 437, 456, 500, 712, and 1338 (claim 3), a premature stop codon (claim 4), a missense mutation (claim 5), a frameshift mutation (claim 6), a splice junction mutation (claim 7), or an insertion mutation (claim 8).

The Final Office Action contends that Applicants have not described a sufficient number of species of APC mutations detectable by antibodies to satisfy the written description requirement. In determining whether the specification meets the written description requirement for the claimed invention "[t]he primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In*

re Wertheim, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). The facts regarding the nature of the invention of claims 2-8 and the teachings of the specification demonstrate that the claimed invention is adequately described.

First, the invention to which claims 2-8 are directed is a preparation of antibodies. Antibodies typically are described by reference to the antigen(s) to which they bind. The U.S. Patent and Trademark Office does not require a written description of antibodies by amino acid sequence or by nucleotide sequence encoding the antibodies. Thus, the Final Office Action's reliance on *Fiers v. Revel* and *The Reagents of the University of California v. Eli Lilly* is misplaced. These cases address the written description of nucleic acids, not antibodies. A discussion of these cases simply is not relevant to written description of a preparation of antibodies.

Second, the present specification imparts to those of skill in the art a substantial amount of information regarding the binding properties of the genus of claimed antibodies, including specific examples of each of the types of mutations encompassed within claim 2 and specifically recited in claims 3-8. The antibodies must specifically bind to a human APC protein that is the product of a mutant allele found in a tumor and must not specifically bind to other human proteins. The human APC protein must be the product of a mutant allele found in a tumor. The human APC protein must be a mutant form of the amino acid sequence shown in SEQ ID NOS:2 and 7. The mutant allele must be a mutant form of the nucleotide sequence shown in SEQ ID NO:1. Finally, the antibodies must not specifically bind to other human proteins. This genus is well circumscribed.

According to the U.S. Patent and Trademark Office's own Written Description Guidelines,

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

66 Fed. Reg. 1099, 1106 (January 5, 2001) (internal references omitted). The types of mutant alleles that will produce mutant APC proteins detectable by the claimed antibody preparations are mutant alleles containing premature stop codons, missense mutations, frameshift mutations, splice junction mutations, and insertion mutations. The specification discloses at least one example of each of these types of mutations:

- an 800 basepair insertion between nucleotides 4424 and 5584 (column 16, lines 52-56);
- an insertion at codon 288 (CCAGT->CCCAGCCAGT) (column 19, Table IIB);
- a point mutation that results in a change from arginine (CGA) to a stop codon (TGA) in codon 331 (column 19, Table IIB);
- a mutation in codon 437 (CAA/gtaa->CAA/gcaa), resulting in a splice donor site (column 19, Table IIB); and
- a point mutation in codon 1338, resulting in a change from Gln (CAG) to a stop codon (TAG) (column 19, Table IIB).
- a C to G transversion at codon 279, resulting in a stop codon (change from TCA to TGA) (column 18, lines 39-44 and Table IIA);
- a point mutation resulting in a change from serine (TCA) to a stop codon (TGA) at codon 712 (column 18, lines 44-46; column 19, Table IIA);
- a point mutation resulting in a change from arginine (CGA) to a stop codon (TGA) at

codon 301 (column 18, Table IIA);

- a point mutation resulting in a change from arginine (CGA) to cysteine (TGC) at codon 413 (column 18, Table IIA);
- a deletion mutation from CAGAG to CAG at codon 243, resulting in a splice-junction (column 19, Table IIA);
- a deletion mutation from CTTTCA to CTTCA at codon 456, resulting in a frameshift (column 19, Table IIA);
- substitution of a T by a G at codon 500, changing the normal tyrosine codon to a stop codon (column 19, Table IIA); and
- a deletion of two adjacent nucleotides, at positions 730 and 731 in the APC cDNA sequence of SEQ ID NO:1 (column 29, lines 3-9).

This disclosure of thirteen specific mutations, including at least one of each of the possible mutations encompassed within claim 2, satisfies the definition of a "representative number of species" set forth in the Written Description Guidelines:

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. . . . What constitutes a representative number is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

66 Fed. Reg. at 1106.

The Final Office Action notes that six of the thirteen specific mutations taught in the specification are truncations. The Final Office Action asserts that truncated APC proteins are identical to wild-type APC proteins except for their shorter length; thus, the Patent and

Trademark Office does not understand how an antibody could be made which can recognize a truncated form but not a wild-type form of APC. Page 4, lines 4-8.

The Final Office Action cites no evidence to support its assertion that truncated APC proteins would be indistinguishable from wild-type APC proteins except for their length. Applicants agree that, up to the point of truncation, the amino acid sequence of a truncated and a wild-type APC protein would be indistinguishable. It does not follow, however, that the three-dimensional conformations of the two proteins would be indistinguishable. As taught in Abbas *et al.*, CELLULAR AND MOLECULAR IMMUNOLOGY, 3d ed., page 51, column 2 (Attachment A), "conformational determinants are formed by amino acid residues from separated portions of the linear amino acid sequence that are spatially juxtaposed only upon folding . . . ." While linear epitopes could remain intact in a truncated APC protein, conformational epitopes could be altered such that an antibody could distinguish between truncated and wild-type proteins. In fact, antibodies can distinguish even between two conformations of the same protein: "When there is more than one stable conformation, antibodies may be specific for one or the other." *Id.* The Final Office Action merely speculates that antibodies could not distinguish between wild-type and truncated APC proteins.

The Final Office Action also asserts that there is no indication that the mutation disclosed at column 16, lines 52-56, translates into a mutation detectable at the amino acid level. This mutation is an 800 basepair insert between nucleotides 4424 and 5584. As indicated in Table 1, the entire 3' end of the cloned APC cDNA (nucleotides 1956 to 8973) "appears to be encoded in one exon, as indicated by restriction endonuclease mapping and sequencing of the cloned genomic DNA." (columns 17 and 18) The Final Office Action speculates that "this insert may constitute only an intron-like sequence which is spliced out prior to protein expression." Page 4,

lines 11-12. No evidence is cited to support this speculation. In fact, many other possibilities exist. For example,

- the 800 basepair insertion could contain a stop codon, resulting in a truncated product;
- the 800 basepair insertion could contain a missense mutation;
- the 800 basepair insertion could contain a frameshift mutation;
- the 800 basepair insertion could contain a splice junction mutation; or
- the 800 basepair insertion could itself be translated, creating an insertion of amino acids in the APC protein.

Each of these possibilities would result in an alteration of the encoded protein detectable at the amino acid level. Thus, even giving the Final Office Action's speculation equal weight with each of the five other possibilities listed above, it is more likely than not that the disclosed 800 baspair insert would result in an alteration of the encoded protein that would be detectable at the amino acid level. Even if, *arguendo*, the Final Office Action's speculation were correct, the specification teaches twelve other specific mutations detectable at the amino acid level. One of the twelve other mutations is an insertion mutation (the insertion at codon 288; see column 19, Table IIB). Thus, the species of mutations described still adequately represent the genus of alleles encoding mutant APC proteins to which the antibody preparations of claim 2 specifically bind. At the time the specification was filed, the skilled artisan would have understood from the disclosure of these representative mutations that the inventors had possession of the genus of antibody preparations that specifically bind to the products of the mutant alleles recited in claim 2.

Claim 3 recites that the mutant allele contains a mutation in one of 11 <u>particular codons</u>.

Mutations in each of these codons are explicitly taught in the specification. See the citations provided above. Nonetheless, the Final Office Action includes claim 3 in the rejection "because, although the claim recites a number of specific mutation loci, the claim is not limited to these loci. The claim is written in an open language format . . . and therefore encompasses any change to the sequence, not just those at the recited loci." Page 3, lines 31-34. Whether or not the recited mutant allele encompasses other changes to the sequence, claim 3 requires that the mutant allele contains a mutation at one of the recited codons and must encode a product to which antibodies specifically bind. Thus, the presence of any other change to the sequence of the mutant allele is irrelevant. Similarly, claims 4-8 each recite a mutant allele that contains a specific type of mutation. Again, examples of each of these types of mutations are taught in the specification. Thus, at a minimum, the rejection should not apply to claims 3-8.

The teachings of the specification regarding the claimed antibodies and the products of the mutant APC alleles to which they specifically bind are substantial. Representative species exemplifying the mutant alleles recited in claims 2-8 are explicitly disclosed. Thus, the written description requirement is satisfied. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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